Different biological aspects have to be considered when estimating the effect of radiotherapy on oligometastases:
1) In contrast to current systemic treatments, radiotherapy has a high potential to inactivate cancer stem cells that are able to cause tumour recurrences. In limited disease stages or, in some cancers, limited metastases stages, this is the basis of the curative potential of radiotherapy and also of complete inactivation of macroscopic metastases.
2) Size of the metastases is predictive for in-field-control. This correlation exists in primary tumours as well as in metastases and reflects the impact of the higher number of cancer stem cells to be inactivated in larger tumours and maybe also higher impact of other resistance factors like hypoxia.
3) Metastases develop through vascular spread of tumour cells, i.e. oligometastases always bear a high risk of later development of further metastases. The time to further disease Progression appears to be longest with a longer time interval between treatment of the primary tumour and development of oligometastases. While this is known for a long time, approaches to biologically characterize tumours with low versus high potential for multi- or oligometastatic spread are only recently developed.
4) Single or oligometastases are often treated using hypofractionated-accelerated radiation treatment schedules, i.e. applying high doses per fraction and higher doses per week as compared to conventionally fractionated radiotherapy schedules. These schedules lead to a higher biological efficacy in the tumour, but also in irradiated normal organs. Thus, for application of high radiation doses, from biological reasons the use of high precision radiotherapy techniques is mandatory to take advantage from the volume-effects in normal tissues that can compensate for the disadvantage of the high doses per fraction.
The talk will give an overview on biological considerations for high-dose radiotherapy of oligometastases and on open questions for further improvement of treatment.

SP-0013
A mathematical model of tumor self-seeding reveals secondary metastatic deposits as drivers of primary tumor growth
P. Gerlee[1], J.G. Scott[2], D. Basanta[3], A.R.A. Anderson[3]
[1]*Göteborg University, Sahlgrenska Cancer Center, Göteborg, Sweden*
[2]*Oxford University, Centre for Mathematical Biology, Oxford, United Kingdom*
[3]*Moffitt Cancer Center, Integrative Mathematical Oncology, Tampa, USA*

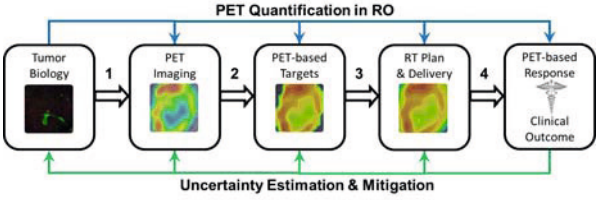
Two models of circulating tumor cell (CTC) dynamics have been proposed to explain the phenomenon of tumor 'self-seeding', whereby CTCs repopulate the primary tumor and accelerate growth: Primary Seeding, where cells from a primary tumor shed into the vasculature and return back to the primary themselves; and Secondary Seeding, where cells from the primary first colonize a secondary tissue which then sheds cells into the vasculature returning to the primary. Thesetwo models are difficult to distinguish experimentally, yet the differences between them is of great importance to both our understanding of the metastatic process and also for designing methods of intervention. Therefore we developed a mathematical model to test the relative likelihood of these two phenomena and show that Secondary Seeding is several orders of magnitude more likely than Primary seeding. We suggest how this difference could effect tumor evolution, progression and therapy and several possible methods of experimental validation.

SYMPOSIUM: PET QUANTIFICATION

SP-0014
How much can we trust PET? (PET uncertainties)
S. Bowen[1]
[1]*University of Washington Medical Center, Departments of Radiation Oncology and Radiology, Seattle WA, USA*

The role of positron emission tomography (PET) in radiation oncology continues to expand beyond the realm of preliminary diagnosis, where FDG PET has directly impacted disease staging in more than 30 % of cancer patients. Radiation oncology clinicians and researchers seek to incorporate PET more objectively into radiotherapy (RT) planning and therapeutic response assessment by leveraging its high sensitivity, tracer specificity, and capacity for absolute quantification. As PET evolves from a qualitative diagnostic tool to a quantitative theragnostic tool, a growing number of clinical trials are evaluating the efficacy of personalized and adaptive RT regimens based on the spatiotemporal dynamics of heterogeneous PET uptake.

However, complex quantitative tasks require the estimation and mitigation of many PET uncertainties. They arise from physical, technical, and biological factors that impact PET lesion signal (contrast) relative to noise, system spatial resolution,and reproducibility. This talk will review uncertainties that determine confidence intervals within which we can trust PET in the context of RT target definition and RT response assessment. In particular, physical uncertainties arising from the image formation process, technical uncertainties from pre- and post-imaging processes, and biological uncertainties from patient-specific tracer kinetics and therapy-induced dynamics will be presented.
The level of trust in PET can be linked to the incorporation of uncertainties into quantification processes. For example, test-retest studies can establish achievable degrees of precision when assessing longitudinal changes in PET metrics. While some uncertainties are mitigated through standardization of imaging procedures within and between institutions, others pose formidable challenges that require innovative technologies and methodologies. Such challenges motivate the need for improved PET quantification and seamless integration into RT planning through multidisciplinary collaboration.



Example workflow of PET quantification tasks in radiation oncology. From tumor biology at the cellular scale to PET-based target definition and therapy response assessment at the image voxel scale, quantitative tasks carry uncertainties that must be estimated and mitigated. This talk will focus on uncertainties in Steps 1 and 2 in the context of their impact on downstream components.

SP-0015
How to make PET more quantitative (PET QA)
R. Boellaard[1]
[1]*VU University Medical Center, Radiology and Nuclear Medicine, Amsterdam, The Netherlands*

PET is a functional and molecular imaging modality allowing to measure (biological) tumor characteristics quantitatively. The most commonly used parameter to quantify tumor tracer uptake is the so-called maximum standardized uptake value (SUVmax). Yet, various other parameters may be of interest. Metabolically active tumor volume (MATV), total tumor burden (sum of MATV over all lesions) or total lesion glycolysis (TLG, product of MATV and SUV) have shown value as predictive or prognostic factor. Beyond measuring glucose consumption with ^{18}F-FDG there is increased interest in the use of other tracers and/or labeled drugs. Proliferation measured with ^{18}F-FLT or hypoxia measured with e.g. ^{18}F-AZA can be of particular interest in a radiotherapy setting. Specific imaging procedure optimizations may be required when using non-FDG PET tracers. In addition, use of simplified (static) image procedures and data analysis methods may need to be validated against full kinetic analysis to determine use of e.g. SUV as appropriate surrogate for the physiological parameter of interest. Full kinetic analysis can then be helpful to determine which simplified quantitative measure is providing the most accurate and robust results. For example, tumor to blood ratios may be more suitable than SUV measures and SUV normalized by body weight may be suboptimal compared to other normalizations, such as body surface area, depending on the biodistribution of the tracer.
All quantitative PET measures, however, depend largely on the way PET images are collected, reconstructed and analyzed. Moreover, new image reconstruction technologies, that include resolution recovery, can improved image resolution and contrast recovery, but at the same time suffer from increased upward bias when PET images are quantified using the maximum standardized uptake value. Consequently, when implementing new PET imaging technologies one should also adapt data analysis procedures in order to obtain and maintain robust quantitative data.
When quantitative PET studies are performed as part of multicenter studies it is not only essential to optimize the PET imaging and data analysis procedure for the specific question to be addressed, but also to make sure that studies are performed in a standardized manner and that all scanner performances are harmonized to a common standard. There are various organizations that offer scanner validation or accreditation (QC) programs. Most of these programs recognize the need not only to verify the basic calibration and uniformity of the PET

images but also underline the need for harmonizing image resolution and data analysis methodology to ensure harmonized quantitative performance across multiple sites.
This lecture will focus on the impact and interplay of image resolution, noise and data collection and analysis methodology on the various ways of PET tracer uptake quantification. Moreover, the impact of relatively new PET technologies, such as time of flight technology and new image reconstruction algorithm, on the accuracy and precision of tracer uptake quantification will be addressed. Finally, based on the first results obtained from the EARL accreditation program, the feasibility and need for a central QA/QC accreditation program will be discussed.

SP-0016
How to integrate PET in radiotherapy planning
G. Cattaneo[1]
[1]*San Raffaele Scientific Institute, Department of Medical Physics, Milano, Italy*

The role of positron emission tomography (PET) scanning in radiation oncology has evolved as it is the most specific and sensitive means of imaging fundamental aspects of tumour biology.
PET has been applied in different RT procedures: correct staging and optimal treatment strategy, accurate delineation of biological target volume (BTV) for treatment planning, prediction of tumor response, evaluation of healthy tissue function after radiotherapy.
In the era of high-precision radiotherapy, accurate tumor volume delineation regarding tumor boundaries, shape and volume is crucial. Quite different approaches have been used for target volume delineation on PET images: the anatomic sites of the pathologic zones on PET scan were delineated on CT scan, absolute/relative thresholding algorithms, complex algorithms (i.e. gradient/statistical based methods).
The introduction of the combined PET/CT imaging modalities into routine clinical RT practice has promise to be of great clinical significance in the accurate delineation of RT target volume in the treatment of cervix, head and neck, and lung cancers.
The overall sensitivity, specificity and accuracy of FDG-PET for detection of lung cancers are very high for primary, residual and recurrent disease; contour guided by FDG-PET/CT led to significant modification of treatment strategy and radiotherapy planning in NSCLC patients. A limiting factor to the accuracy of target volume definition by PET/CT is organ and tumor motion, which is mainly due to the patient respiration. Motion management is thus becoming an important issue in both diagnostic and RT applications, particularly when PET/CT images are used for tumor delineation; within this contest 4D techniques provide information which can be used to improve/personalize volume definition and treatment planning strategy.
Careful comparison of FDG-PET, MRI and CT scans with the histopathology of resented tumor specimens shows is the most accurate of the three for the detection of head and neck cancer.
PET images are used for tumor detection and delineation, however such images may also contain information on the spatial distribution of factors influencing tumor radiosensitivity (hypoxia, proliferation) and a few studies have used PET in biologic image-guided dose escalation to the radioresistant BTV using IMRT. This use of PET imaging in combination with dose escalation is of great interest in tumor sites such as head-and-neck and the prostate.

SYMPOSIUM: DOSIMETRY OF LOW AND MEDIUM ENERGY PHOTON BEAMS IN RADIOTHERAPY

SP-0017
Reference dosimetry in low and medium energy x-rays from air kerma to dose to water standards
P. Mayles[1]
[1]*Clatterbridge Cancer Centre, Physics, Liverpool, United Kingdom*

Kilovoltage x-rays are something of a Cinderella subject in radiotherapy physics although accurate absolute dosimetry is perhaps more challenging than for megavoltage beams.
The first step is to determine the energy/quality of the beam. This is usually done in terms of the first half value layer (HVL) measured under narrow beam conditions. In order to fully characterise the energy spectrum the generating kV is also needed and TG-61 shows that there is wide variation in the HVL for the same generating potential. The IAEA defines low energy as up to a generating potential of 100 kV or 3 mm of Al HVL and medium energy as starting at 80kV or 2mm of Al. The IPEM defined an additional very low energy band from 0.035 mm of Al up to 1 mm (8-50kV) with low energy considered as up to 160kV.
Most standards laboratories offer only an air kerma calibration based on ionometry, but PTB also has a calorimetric standard. The IAEA TRS398 code of practice offers a formalism for the use of a calibration factor defined in terms of absorbed dose to water and suggests that standards laboratories that offer only an air kerma calibration could also provide calibrations in terms of absorbed dose to water by applying an appropriate air kerma code of practice. In IAEA TECDOC1455 comparing TRS398 to air kerma based codes of practice differences of up to 4% were found for low energies but agreement was within 1% for medium energies.
There are two ways in which the output of the machine can then be measured: a measurement of air kerma in air together with the application of a backscatter factor or a calibration at a relevant depth in a phantom. In the latter case a perturbation correction is needed. The magnitude of these corrections is calculated using Monte Carlo methods. Changes to codes of practice of around 7% (at 100kV) have been required (IAEA TRS277 and IPEMB revision 2005). The consensus seems to be that measurement at 20 mm depth in water is the preferred approach for medium energy x-rays but codes of practice are divided about whether measurements at very low energy (40kV) should be in air (e.g. TG61) or a phantom (e.g. IPEMB). There is general agreement that plastic phantoms need to be used with care.
Newer devices such as the Zeiss Intrabeam device and the Ariane Papillon machine use 50kV x-rays with more challenging geometries. For these devices special jigs are needed to ensure geometric accuracy and GafChromic EBT2 film may also offer an appropriate means of reference dosimetry especially for small fields. For low energies the requirement for controlled geometry suggests the use of plastic phantoms but for medium energies the use of liquid water reduces uncertainty.

SP-0018
Monte Carlo for low and medium energy x-ray beam modelling
C. Ma[1]
[1]*Fox Chase Cancer Center, Radiation Oncology, Philadelphia PA, USA*

Purpose/Objective: The Monte Carlo method is the most accurate method for radiation measurement simulation and dose calculation. This presentation reviews the recent advances of Monte Carlo for low and medium energy x-ray beam modeling.
Material/methods: In the last 20 years significant developments have been made in the areas of radiation transport theory, Monte Carlo simulation techniques and computer technology, which have enabled the Monte Carlo method for widespread applications in radiation measurement and clinical radiotherapy dosimetry. Kilovoltage x-rays are different from megavoltage x-rays due to their excessive scattering properties and short electron ranges,which make it possible to simulate photon transport only in some Monte Carlo applications such as brachytherapy dose calculation.
Results: We will first start with the Monte Carlo modeling of the air-filled ionization chamber response in low and medium energy x-ray beams where the fractional contributions of the secondary electrons from the cavity air and the surrounding chamber media were investigated accurately. This will be followed by Monte Carlo studies of ionization chamber corrections factors for the chamber stem and waterproofing sheath that demonstrated the accuracy and efficiency of Monte Carlo simulations of the photon attenuation and scattering effects with the use of correlated sampling techniques. More detailed reviews of the Monte Carlo method for radiotherapy dosimetry and treatment planning will be given with a focus on radiation source modeling, kilovoltage CT dose calculation, and treatment planning dose calculation for external beam therapy and brachytherapy.
Conclusion: The Monte Carlo method has been demonstrated as a useful simulation tool for accurate dosimetry measurement and radiotherapy dose calculation.

SP-0019
Radiobiology of kilovoltage x-rays
A. Nahum[1]
[1]*Clatterbridge Cancer Centre, Physics, Bebington, United Kingdom*

X-ray beams with peak energies ranging from around 50 to 300 kilovolts were in widespread use until the end of the 1950s when Cobalt 60 gamma rays and accelerator produced megavoltage x rays took over due to their much greater penetrating power. However, almost all of our knowledge of (cellular) radiobiology has been derived from irradiating cells with kilovoltage x ray sources, for reasons of cost and practicability. It is therefore essential that we do not forget about their radiobiological properties, even if such radiation qualities play only a minor role in today's radiotherapy. Furthermore, the differences in cell killing between kilovoltage and megavoltage photons (and electrons) per unit dose have a great deal to teach us about the fundamental mechanisms of the biological effect of radiation.